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Original Article

Novel validated stability-indicating UPLC method for the determination of Metoclopramide and its degradation impurities in API and pharmaceutical dosage form

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ABSTRACT

Aim: To develop a stability-indicating reversed phase ultra performance liquid chromatographic (RP-UPLC) method for the determination of related substances in Metoclopramide bulk drugs and pharmaceutical dosage form.

Method: The chromatographic separation was achieved using a Waters X-terra RP18 (150 × 4.6 mm), 3.5 μm particle size column using the gradient program with mobile phase consisting of solvent A: 30 mM monobasic sodium phosphate and 2.3 mM of pentane-1-sulphonic acid sodium salt (pH 3.0 buffer) and solvent-B (Acetonitrile). A flow rate of 1.2 mL/min and UV detector at 273 nm was used. The runtime was 18 min within which Metoclopramide and its four impurities, ACETYLMETO, ACMA, CLEE and ACME were well separated.

Results and discussion: The drug was subjected to stress conditions such as oxidative, acid & base hydrolysis, thermal and photolytic degradation. Metoclopramide was found to degrade significantly in photolytic, oxidative & thermal stress conditions and stable in acid, base, hydrolytic & humidity stress conditions. The major degradation impurities in oxidation and photolytic degradation were identified by LCMS. The degradation products were well resolved from the main peak and its impurities, thus proved the stability-indicating power of the method.

Conclusion: The developed method was validated as per ICH guidelines with respect to specificity, linearity, limit of detection, limit of quantification, accuracy, precision and robustness. The calibration curves obtained for the four impurities were linear over the range 0.062–3.040 μg/mL.

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1. Introduction

Metoclopramide is chemically 4-amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-methoxybenzamide, an antiemetic and gastroprokinetic agent. It is commonly used to treat nausea and vomiting, to facilitate gastric emptying in people with gastroparesis, and as a treatment for gastric stasis often associated with migraine headaches. The antiemetic action of Metoclopramide is due to its antagonist activity at D2 receptors in the chemoreceptor trigger zone (CTZ) in the central nervous system (CNS)—this action prevents nausea and vomiting triggered by most stimuli.[1] At higher doses, 5-HT3 antagonist activity may also contribute to the antiemetic effect. The gastroprokinetic activity of Metoclopramide is mediated by muscarinic activity, D2 receptor antagonist activity and 5-HT4 receptor agonist activity.[2] Metoclopramide is freely soluble in water and ethanol and practically insoluble in ether. The molecular formula is $C_{14}H_{22}ClN_3O_2$, which corresponds to a molecular weight of 299.80.

Very few analytical methods have been reported for the quantitative determination of Metoclopramide in formulations as well as biological fluids. These include gas chromatography[3,4] and high performance liquid chromatography.[5,6] These previously published methods comprise of complicated mobile systems and are not directly applicable for this novel type of dosage form which is prepared and need more investigation for method development and validation. However, no stability indicating UPLC methods were reported to estimate Metoclopramide and its degradation products (Fig. 1). The proposed method was stability indicating by which all the degradation products of Metoclopramide can be estimated quantitatively at very low levels.

2. Experimental

2.1. Chemicals and reagents

Metoclopramide (purity 99.0%) and standard materials of degradation products were obtained from Hospira Health Care India Pvt Ltd, Chennai, India. Monobasic sodium phosphate, pentane-1-sulfonic acid sodium salt, orthophosphoric acid and acetonitrile were purchased from Ranbaxy Chemicals, New Delhi, India and all are of HPLC grade. Water was purified by milli-Q-water purification system (Millipore, Bedford, MA, USA) and used for preparation of all the solutions.

2.2. UPLC instrumentation and condition

The analysis was performed using Waters Acquity system equipped with a binary solvent delivery pump and PDA detector. Data acquisition and processing were done by using Empower2 software version FR5 (Waters Corporation, USA). The chromatographic separation was performed using a Waters X-terra RP18 column (150 × 4.6 mm), 3.5 μ particle column. The mobile phase was a mixture of mobile phase A and mobile phase B. Mobile phase A was mono sodium phosphate (3.4 g/L) and pentane-1-sulfonic acid sodium salt (0.4 g/L) adjusted to pH 3.0 with orthophosphoric acid and acetonitrile as mobile phase B. The gradient program T (min) = % B: 0 = 10, 2 = 15, 5 = 17, 7 = 20, 8 = 25, 9 = 30, 13 = 25, 15 = 10, and 18 = 10, with flow rate of 1.2 mL/min was employed. The injection volume was 10 μL while the detector was set at 273 nm. The column temperature was maintained at 35 °C.

2.2.1. Preparation of buffer, diluent, standard and sample solution

About 3.4 g of monobasic sodium phosphate dissolved in 800 mL of water, adjusted to pH 3.5 ± 0.05 with dilute orthophosphoric acid solution was used as buffer. The diluent used was a mixture of buffer, acetonitrile and water in the ratio of 80:15:5 (v/v/v).

A stock solution of Metoclopramide Hydrochloride (240 μg/mL) was prepared by dissolving an appropriate amount in the diluent. Standard solution containing 6 μg/mL was prepared from this stock solution. 5 mL of Metoclopramide injection USP solution containing 5000 μg/mL was dissolved in 25 mL of diluent to give a solution containing 1000 μg/mL as sample solution.

2.3. Forced degradation sample solution for specificity study

The study was intended to ensure the separation of Metoclopramide and its degradation impurities. Forced degradation

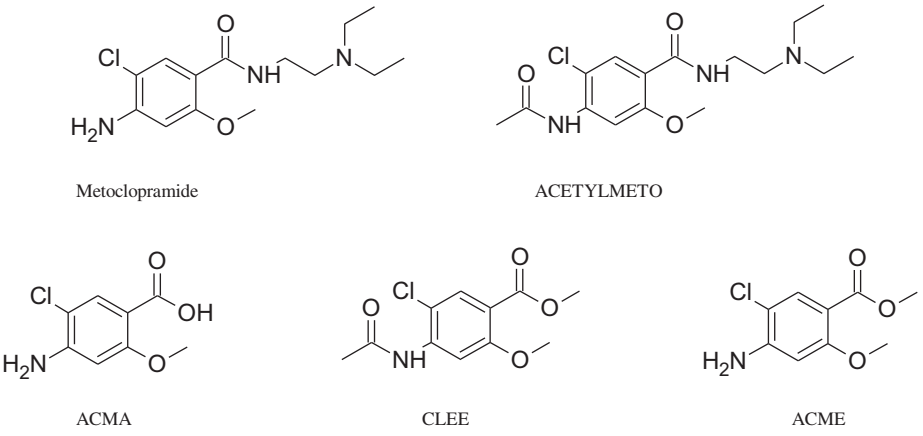

Fig. 1 – Structures of Metoclopramide and its impurities.